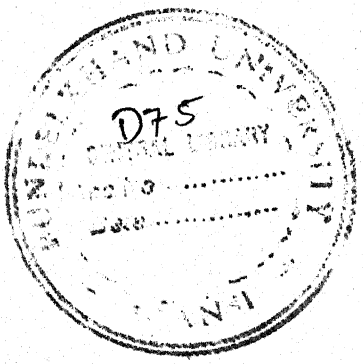
Peribulbar Anaesthesia - With Alkalinization And/Or Hyaluronidase : A Comparative Study

THESIS
FOR

MASTER OF SURGERY
(OPHTHALMOLOGY)



M.L.B. MEDICAL COLLEGE
BUNDELKHAND UNIVERSITY,
JHANSI (U.P.)

2003 **ARSHIA MATIN**

DEDICATED
TO MY
PARENTS

DEPARTMENT OF OPHTHALMOLOGY

M.L.B. MEDICAL COLLEGE, JHANSI

CERTIFICATE

This is to certify that the work entitled "***Peribulbar Anaesthesia – With Alkalinization and / or Hyaluronidase: A Comparative Study***", which is being submitted as a thesis for M.S. (Ophthalmology) examination 2003 of Bundelkhand University by Dr. Arshia Matin, has been carried out in the Department of Ophthalmology, M.L.B. Medical College, Jhansi.

She has put in the necessary stay in the department as per university regulations.

Dated : 30·4·2003

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The work has been carried out under my direct supervision and guidance. The techniques and statistical methods used in this thesis have been undertaken by the candidate herself and checked by me from time to time.

She has put in the necessary stay in the department as per university regulations.

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Certificate

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"The habits of punctuality, order, diligence, determination and concentration are the key to success." This is what has been inculcated into us by our honourable Head of Department and my Guide, Dr. B.S. Jain M.S., Department of Ophthalmology, M.L.B. Medical College, Jhansi. His sense of precision, inflinching tenacity, passion for reason, compassion towards patients, knowledge and experience was a constant source of inspiration to me. It was under his able guidance I read, learned and ventured to write. Still, I take this opportunity to acknowledge most humbly with a deep sense of gratitude my indebtness to him. His encouragement helped me to carry out this present work.

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I wish to express my sincere gratitude to my patients whose co-operation is an essential part of any study.

With this I humbly submit this work as a step in the progress of ocular anaesthesia.

Arshia Matin

Dated : 30·4·2003

Dr. Arshia Matin

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** Summary in Separate cover**

INTRODUCTION

INTRODUCTION

To keep pace with the rapid advances in ophthalmic surgery, the race is now on towards faster, safer and effective ocular anaesthesia. General anaesthesia introduced in 1846 was not welcomed by the ophthalmic surgeon because it made the operation more difficult due to orbital congestion, and the extra time necessary for the patient to be made ready. Additionally, the proximity of the anesthetist to the surgical field, trying to keep the patient breathing and motionless added to the difficulties. Besides, general anaesthesia carried the risk of death.

The concept of ocular anaesthesia dates back to 1884, when Carl Koller first reported the use of topical cocaine in producing complete ocular anaesthesia. Cocaine abolished pain even though it did not keep the lids and the eye immobile. However, topical cocaine did not diffuse deep enough to abolish sensations from the iris in most patients and did not eliminate pain from pull on the muscles or the cutting of the optic nerve.

The technique of retrobulbar anaesthesia has been described as early as 1884 by Knapp but this form of ocular anaesthesia alone left the lids mobile or required a supplement injection to make them immobile, besides its many complications.

But surgical anaesthesia with accompanying akinesia of the globe and eyelids are the objectives while performing eye surgery and this can be achieved by the peribulbar block.

Drs. Davis and Mandel, with their publication of peribulbar anaesthesia in 1986, startled the ophthalmic world using an alternative term for injections of anaesthetic blocks behind the eye-namely, peribulbar anaesthesia. In their original publication, a 35 to 38 mm Atkinson short bevelled needle was placed deep in the orbit in the periorbital space in the infero-temporal and supero-nasal quadrants, instead of in the muscle cone.

Peribulbar anaesthesia is a valuable addition to ophthalmic surgery for it eliminates the serious side effects, though few. These complications include retrobulbar haemorrhage, respiratory depression, intradural or subarachnoid injection, optic nerve damage and perforation of the globe.

Contrary to retrobulbar block the effect of peribulbar block is slow, because the anaesthetic agent is deposited outside the muscle cone and must diffuse through various tissue barriers before reaching the nerve membrane. Therefore, frequent clinical problems associated with the peribulbar block are, increased time of onset for anaesthesia and akinesia of the eye, higher initial failure rate and higher volume of local anaesthetic used when compared with retrobulbar block. Because of incomplete anaesthesia, further injections are often required.

To overcome this shortcoming Meyer and associates first isolated the enzyme hyaluronidase. Later, studies established the fact that the addition of hyaluronidase caused a rapid dispersion of fluid when injected into tissues. This was brought about by

depolymerization and hydrolysis of hyaluronic acid gel. The reduction in viscosity removes one of the barriers to diffusion of fluid and allows it to permeate the tissue more rapidly and widely resulting in a shorter onset time for anaesthesia and akinesia in peribulbar block.

As efforts to overcome the slow onset of anaesthesia together with prolonging the duration of anaesthesia continued, different researchers suggested that relative alkalinity of the local anaesthetic agent can be a major determining factor in altering the onset and duration of the block.

Addition of sodium bicarbonate to local anaesthetic solution results in an increase in the pH of the local anaesthetic solution, leading to an increase of the drug in the uncharged base form, which is the form more permeable to the nerve sheath and nerve membrane thereby resulting in a more rapid onset of the block.

This inspired us to conduct a study to evaluate the effect of alkalinization and/or hyaluronidase with lignocaine hydrochloride and adrenaline in peribulbar block.

AIM OF STUDY

AIM OF STUDY

To evaluate the effect of sodium bicarbonate and/or hyaluronidase with lignocaine hydrochloride and adrenaline on onset and duration of peribulbar block.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Ophthalmic surgery has been performed since the time of Greeks, Egyptians and Arabs much before the advent of any form of anaesthesia. Lid surgery by cauterization for ectropion and entropion was one of the earliest ophthalmic surgeries. Cataract operations were done by a process known as 'reclination', more commonly known as couching.

In the year 1800, Humprey Davy described the anaesthetic properties of nitrous oxide and suggested its use for surgical procedures. In 1846 Morton successfully demonstrated the use of ether for anaesthetic purposes.

Early Local Anaesthetics:

The early Egyptians are said to have rubbed the powdered skin or fat of crocodile upon the patients skin to produce local anaesthesia, but without much success (Atkinson, 1943).

Cocaine:

Gaedeke in 1855 was the first to discover the alkaloid of coca leaves and called it Erythroxylin. (Atkinson, 1943).

The use of cocaine for ophthalmic purpose was demonstrated in 1884, for the first time by a young Austrian resident in ophthalmology – Carl Koller. Koller prepared aqueous solutions of cocaine and proved its anaesthetic potency in animal and human eyes (Feibel, 1989).

Nerve block and discovery of procaine:

The infiltration of cocaine near or into nerve was reported by Hall and Halsted in 1884 and yet it was not until thirty years after this report that 'Van Lint' in 1914 thought of blocking the facial nerve to produce akinesia of orbicularis.

In 1899, the discovery of the chemical composition of cocaine and its atomic groups by 'Einhorn' made its synthetic preparation possible. This lead to discovery of procaine by Einhoxin in 1905.

Epinephrine:

In 1901, Tikamine isolated the active salts of the suprarenal gland and named them as epinephrine. The contribution increased greatly the efficacy of local anaesthesia and facilitated operative procedures in which considerable bleeding is encountered (Atkinson, 1943).

The year 1940 saw the start of the next major advance. Working in Stockholm on the structure of the alkaloid gramine, Erdtman – an organic chemist, tasted one of the substances that had been produced as a precursor of gramine. The significance of ensuing numbness was appreciated immediately and the search for a chemically useful derivative was started by Erdtman and continued by Lofgren who synthesized lignocaine in 1943. Lofgren in 1948 laid the foundation of subsequent studies of local anaesthetic drugs.

Ophthalmic Anaesthesia:

In 1884, Herman Knapp of New York was the first one to describe retrobulbar anaesthesia in enucleation surgery (Atkinson, 1943; Feibel, 1989; Friedberg, 1989).

Van Lint in 1914 popularized the use of procaine for facial block but only in 1930's did the use of procaine for retrobulbar anaesthesia became widespread (Atkinson, 1943).

Atkinson in 1949, in his preliminary report on the use of hyaluronidase with local anaesthesia in ophthalmology reported that with hyaluronidase added to the anaesthetic solution, there is less ballooning of the tissues, due to rapid diffusion, and not as much procaine solution is required to produce the anesthesia.

Atkinson (1943) advocated the use of a 22 gage needle, 3.5 cm long for deeper injections, such as retrobulbar injection within the muscle cone and blocking of the lid.

Retrobulbar anaesthesia, a common form of anaesthesia, has numerous complications associated with it. These include central retinal artery occlusion (Klein et al, 1982), perforation of the globe(Duker et al, 1991), contralateral amaurosis (Friedberg et al, 1986), direct needle injury to posterior ciliary arteries, ophthalmic artery or optic nerve (Ellis, 1974; Edward B. Mclean, 1975).

Davis and Mandel in 1986, introduced the peribulbar anaesthesia which eliminates the serious side effects of retrobulbar block.

Various pharmacological as well as technical advances are still advocated to increase the efficacy, duration, safety and reduce complications of regional ocular anaesthesia.

Ritchie and Greengard (1965) suggested that it is the lipid soluble moiety of the local anaesthetic agent which is more concerned with the penetration of tissue barriers and that the electrically charged cation form is probably the active agent that finally engages at the charged surface of an excitable membrane.

Bromage P.R. et al (1967) demonstrated improved quality of block when carbon dioxide enriched local anaesthetic was injected epidurally, and concluded that this was not due to greater concentration of anaesthetic cation at the nerve axon but due to direct stabilizing effect of carbon dioxide on excitable tissues.

Bromage P.R. et al (1972) sought for the latency and duration of supraclavicular brachial block in 183 patients using carbonated lignocaine and bupivacaine hydrochloride. He found that carbonated lignocaine had the shortest latency and duration. Bupivacaine had longest latency and duration, while mixture of both carbonated lignocaine and bupivacaine hydrochloride produced rapid onset with moderately longer duration.

Gary Strichartz (1976) concluded that local anaesthetics block nerve conduction by preventing the increase in membrane permeability to sodium ions and it is the cationic protonated form that appears to be more active than the neutral form.

Alon, P. Winnie, Cheng – Hin Tay et al (1977) described a new model for the study of pharmacokinetics of local anaesthetics which allows the separate determination of onset and recovery of sensory and motor block in peripheral (mantle) and central (core) bundles within the nerve trunks. In his study he concluded that motor fibres located peripherally blocked first and were last to recover in comparison to sensory fibres situated centrally.

Daniel C. Moore (1981) reported the pH values of the commonly used, commercially prepared local anaesthetic agent with and without epinephrine 1 : 200,000 as well as additives that they contain by the Beckman model 3560 digital pH meter. With the exception of chlorprocaine, all solutions of the local anaesthetic drugs without epinephrine had pH values of 4 or greater and solution with epinephrine had pH values less than 4. In his study he specified that 2% lignocaine without epinephrine has pH of 6.32, while commercially prepared 2% lignocaine with epinephrine has a pH of 3.86.

Hilger M. (1985) in a double blind study compared 0.5% bupivacaine with epinephrine 1:200,000 (pH 3.9) with an alkalinized solution of bupivacaine with epinephrine 1:200,000 (pH 6.4) when used for brachial plexus block. He reported that alkalinization of bupivacaine solution increased the onset and prolonged duration of sensory block.

Radha Sukhani and Alon P. Winnie (1987) experimented in fifty healthy patients undergoing upper extremity surgery by

subclavian perivascular technique. They compared carbonated lignocaine and lignocaine hydrochloride and found that the carbonated lignocaine reduced the latency of anaesthesia by 45% as compared with its hydrochloride salt, producing complete motor block in almost as many as twice patients. The duration of anaesthesia provided by the two agents was virtually identical as was duration of motor block. They concluded this due to the liberation of carbondioxide from the carbonated solution which diffuses very rapidly across a nerve membrane causing a fall in the intracellular pH, and the production of cationic trap which results in marked increase in the amount of active cation available at the receptor sites on the sodium channels inside the nerve membrane. Furthermore carbon dioxide may also have a direct stabilizing effect on the nerve membranes.

Zahl K. et al (1989) undertook a prospective, double masked, randomized study to see if a pH adjusted mixture of lidocaine, bupivacaine and hyaluronidase had faster and more complete onset of neural blockade, when used for peribulbar anaesthesia. Eighty patients were randomly assigned to four groups and received a peribulbar block with one of four mixture: group 1 (L) = 2% lidocaine, group 2 (LPH) = 2% lidocaine with 0.06meq/ml sodium bicarbonate, group 3 (LE) = 2% lidocaine with 1 : 100,000 epinephrine (commercially prepared), or group 4 (LEPH) = 2% lidocaine with 1 : 100,000 epinephrine with 0.06 meq / ml sodium bicarbonate. To 5ml of each of the preceding groups, 5ml of 0.75% bupivacaine and 150 units of hyaluronidase was added. After each block, extraocular muscle movement was followed in each quadrant until akinesia developed. In the event of incomplete akinesia, blocks were supplemented at 20

minutes. The LPH group had the fastest onset to complete akinesia (7.0 ± 2.0 minutes, mean ± SEM) when compared with the onset time of all other groups (group 1 = 11.5 ± 1.9 minutes, group 4 = 13.1 ± 1.4 minutes, and group 3 = 16 ± 1.8 minutes, significance greater than 95% by analysis of variance). Further move, when compared with group 3 by analysis of variance, group 4 had a faster onset time. The authors concluded that pH adjustment of solutions of lidocaine / bupivacaine / hyaluronidase, with or without epinephrine improved the onset time of peribulbar anaesthesia.

Scott G. Eccarius et al (1990) conducted a double – masked, randomized clinical trial to determine if subcutaneous eyelid injections of a bicarbonate – buffered lidocaine – epinephrine – hyaluronidase mixture were less painful than unbuffered injections. Twenty-one patients received both buffered (pH = 7.4) and unbuffered (pH = 4.6) injections. After each injection, patients recorded pain on a scale of O, "no pain," to 10, "severe pain". Mean pain score for buffered injection was 2.0 versus 4.1 for unbuffered injections (P = 0.0003). Seventeen (81%) of 21 patients ranked the buffered injection less painful. They concluded that use of a buffered (pH = 7.4) mixture is effective in making ophthalmic anaesthesia less painful.

Lewis P. et al (1992) carried out a random comparison of plain with pH – adjusted bupivacaine with hyaluronidase for peribulbar block. 50 patients scheduled for cataract surgery received either plain (pH 5.4) or pH – adjusted (pH 6.8 range 6.7 – 6.9) 0.75% bupivacaine. Hyaluronidase was added to both solutions prior to peribulbar block. The time of onset of akinesia of the globe and the need for supplementary injections were recorded by an independent observer.

Patients who returned for surgery to the second eye received the alternative local aneasthetic solution for the second peribulbar block. The relative efficacy for the different anaesthetic solutions was compared in patients who underwent unilateral surgery (Group A, n = 50). In 12 patients (Group B) who underwent bilateral surgery, direct comparisons between eyes in the same patient were possible.

In both groups of patients, eyes receiving peribulbar block with the pH – adjusted solution showed a shorter time to partial akinesia of the globe ($P < 0.05$) (Group A : 5.7 ± 1.76 minutes for 23 patients who received pH – adjusted solution against 6.9 ± 1.98 minutes for 24 patients who received plain bupivacaine solution). However, there was no difference between the solutions in the time to complete akinesia of the globe (Group A : 10.7 ± 4.8 min for 17 patients who received plain bupivacaine solution against 8.5 ± 2.7 minutes for 18 patients who received pH – adjusted solution), but the number of supplementary injections required for an effective block with pH – adjusted solution was increased (9 out of 26 in the plain versus 13 out 24 in the pH – adjusted solution). Onset time to akinesia of the lateral and superior rectus muscles was shortened in patients receiving the pH – adjusted solution but there was minimal effects on the medial and inferior recti.

Roberts JE, Macleod BA and Holands RH (1993) carried out a double blind study to determine the effect of pH and the addition of hyaluronidase to a mixture of lignocaine and bupivacaine on the efficacy of peribulbar anaesthesia. One hundred patients were assigned to one of five groups. All group received a solution of two parts bupivacaine (0.75%) and one part lidocaine (2%) (with 1: 100,000 adrenaline) as the base components of their anaesthesia. Group 1 received only the bupivacaine – lidocaine mixture, pH 3.9. Group 2 received a solution supplemented with

hyaluronidase (ten units. ml^{-1}) pH of 5.1. Group 3 received the bupivacaine – lidocaine mixture alkalinized with sodium bicarbonate to a pH of 5.1, the same as solution 2. Group 4 received the mixture with hyaluronidase alkalinized to pH of 6.7. Group 5 received the bupivacaine-lidocaine mixture alkalinized to a pH of 6.7. Efficacy of each block was graded according to the degree of residual movement 30minutes following injection as described by House et al. The solution containing hyaluronidase and pH adjusted to 6.7 was found to be the most effective ($P < 0.025$) (2 out of 20 failed blocks against 9 out of 20 in Group 3 and 11 out 20 in Group 1, 2 and 5.). No differences were found in the incidence of failed blocks among the other groups. Similarly, group 4 had a lower mean motor score ($P < 0.05$) than the other groups, but no difference existed among the other groups. Thus presence of hyaluronidase without alkalinization did not improve the efficacy and similarly, alkalinization in the absence of hyaluronidase was ineffective.

Martin Zehetmayer, et al (1997) compared the efficacy of a sodium-bicarbonate adjusted preparation of lidocaine 4% (pH = 7.2) and standard lidocaine (pH = 5.2) for topical anaesthesia in clear corneal cataract surgery. They included 44 eyes of 34 patients in this study. In 22 eyes, pH – adjusted lidocaine 4% was administered; in the other 22, standard lidocaine 4%. Aqueous and serum concentrations of lidocaine were measured by high – performance liquid chromatography and ultraviolet detection. Subjective pain was assessed using a visual analog scale of no pain (0%) to worst imaginable pain (100%). On the first postoperative day, visual acuity, IOP and corneal staining with fluorescein were examined. In the pH – adjusted lidocaine group, significantly higher lidocaine concentrations were found in the aqueous humor (15.06μg/ml $\pm$ 8.2 versus 4.75 $\pm$

3.5μg/ml; P < 0.0001). In all samples (n = 8), serum lidocaine concentration were below a minimum detectable level of 0.02μg/ml. Subjective pain ratings were similar in the pH- adjusted and standard lidocaine groups (mean 9.73 ± 10.4% and 10.0 ± 15.4% respectively).

In their study, they concluded that pH – adjusted lidocaine 4% was a safe, effective topical anaesthetic for clear corneal surgery and has minimal local and systemic toxicity. Admiministration of pH adjusted lidocaine 4% resulted in significantly higher aqueous humor lidocaine concentration than administration of standard lidocaine 4%.

Mack YH Chow, Alex TH Sia, CK Koay and YW Chan (1998) assessed the onset of sensory and motor block as well as the distribution of sensory block after axillary brachial plexus block. 1.5% lignocaine hydrochloride containing adrenaline (1:200,000) with and without sodium bicarbonate was given in 38 patients and they found that alkalinization of lignocaine did not offer a significant clinical advantage in axillary brachial plexus block.

Ririe DG, Walker FO, James RL, and Butterworth J (2000) performed median nerve blocks in 10 volunteers in a randomized, double blind cross over study to compare the effects of 1% plain lignocaine with 1% lignocaine mixed with sodium bicarbonate 0.1 mmol/liter. Sensations of hot, cold, pin prick, light touch and motor sensations were assessed at two minute intervals. pH was 6.4 ± 0.1 for plain lignocaine and 7.7 ± 0.2 for alkalinized lignocaine. The final data suggested that addition of bicarbonate to lignocaine for median

nerve block significantly increased the rate of motor block without changing the onset or extent of sensory block.

Aim Of Local Anaesthesia In Ophthalmic Surgery

The aim of anaesthesia in ophthalmology is to provide pain relief, akinesia and hypotony, aside from considerations of morbidity and mortality.

The eye should be motionless during surgery to prevent inadvertent rise of intraocular pressure and to provide stability to the surgeon. Any procedure should not be painful for the patient as this will result in sudden movement of his head, disrupting the surgeons stability and concentration.

The feeling of pressure by various manipulations on the eye is unavoidable and this should be explained to the patient.

Any movement of the eyelids should not be present as squeezing of the lids will result in rise of IOP.

Most important is to maintain an IOP at or below normal levels for safe surgery; achieved by applying pressure on the eyeball by one of the various available methods.

The field of surgery should be bloodless. This is achieved by addition of adrenaline.

The patient should be comfortable at all times, preoperatively, during surgery and postoperatively.

THE IDEAL LOCAL ANAESTHETIC

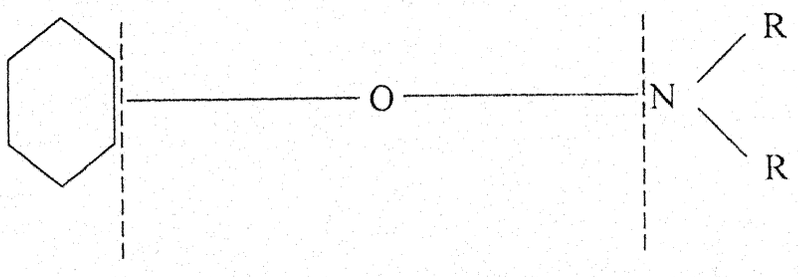
The criteria for an ideal local anaesthetic are : It should be –

- Non – irritating
- Non – pain producing
- No – neurotoxicity
- No toxicity to any of the peripheral organs of the body
- Dissoluble in a sterile and soluble solution.

In this regard the present amide local anaesthetic come close in ophthalmology because of the smaller amounts of local anaesthetic required to render the operative field pain-free and immobile. No clinically useful commercial concentrations of local anaesthetics have been found that produce painless injection. Therefore, the use of a painless dilute solution of local anaesthetic is required to anaesthetize the patient without producing pain; pH adjustment and slow injection alleviate much pain.

PHARMACOLOGY OF LOCAL ANAESTHETIC DRUGS

A local anaesthetic is a drug which reversibly blocks the transmission of peripheral nerve impulses. The agents conform to a common structural arrangement consisting of a benzene ring attached to an amine group by an intermediate chain, which includes either an ester or an amide linkage.



Aromatic Group	Intermediate Chain	Amine Group

Mechanism of Action

During the resting phase the interior of a peripheral nerve axon has a potential diference of about – 70 mv relative to the outside. The resting potential exists because there are more anions then cations within the cell. In the present context the most important ions are sodium and potassium. The high extracellular sodium concentration is maintained because at rest the membrane is impermeable to sodium. However it is freely permeable to potassium ions, which diffuse out of the cell until the negative intracellular electrochemical potential created by their loss balances the concentration gradient.

Depolarization of the fibre is the result of a sudden increase in membrane permeability to sodium. Nerve stimulation causes changes in the configuration of large protein molecules present in the cell membrane resulting in "channels" in these proteins to open and it is through these channels that sodium ions enter the axoplasm. Entry of the positively charged sodium ions raises the membrane potential to about + 20 mv, at this point the electrochemical and concentration gradients for sodium balances one another and the channels close. Both concentration and electrochemical gradients then favour movement of potassium out through the membrane until the resting potential is restored. The impulse generated is transmitted along the axon because a local current flows between the depolarized segment of nerve and the next segment. The voltage change associated with

this current opens the sodium channels in the next section, so that the action potential is propagated along the nerve.

Local anaesthetic drugs prevent the development of the action potential in a nerve by preventing sodium ion movement through the sodium channels.

It is the lipid soluble un-dissolved base form of the drug that penetrates the neuronal membrane to reach the interior of the axoplasm. But the blockade of conduction is produced by the water-soluble dissociated cationic form. The degree of dissociation is dependent on the drug's dissociation constant (pKa). This is the pH at which the drug is present in half undissociated and half dissociated form. The pKa of commonly used local anaesthetics is between 7.6 and 8.9. Most commercial preparations of local anaesthetics are quite acidic to improve stability of the durg and thus prolong its shelf life. At this range of pH less drug is available in the undissociated base form, which is required for transfer of the drug across the perineural sheath and neural membrane. After penetration, the drug re-equilibrate in the axoplasm of the nerve with the charged cationic form. Cationic form of the drug then enters the sodium channel from the intracellular side of the nerve membrane and binds to an anionic site within the sodium channel producing conformational changes in the channel structure. The physical presence of ions and the conformational change in the channel structure block sodium ion movement and prevent depolorization. Agents influencing the degree

of dissociation should therefore have an effect on the onset and degree of neural blockade.

CARBONATED LOCAL ANAESTHETIC SALTS

It has been known for a long time that the hydrogen ion concentration is an important factor in the uptake of local analgesic agents. Begnon in1892 mentioned cocaine with alkali added, and in 1910 Gross suggested how alkalinized solutions worked. The theory of carbonated local analgesics has been aptly put forward by Bromage in 1965.

The theory behind the idea of alkalinizing lignocaine is that like most local anaesthetics, lignocaine is a weak base with a pKa of 7.9. Despite being a weak base it is commercially available as an acidic solution. This is done to increase its stability and shelf-life. The acidic solution has more drug in the ionized form. When used in nerve block, the anaesthetic solution has to cross the perineural sheath and nerve membrane. The non-ionized or the base form of the local anaesthetic is permeable to these structures, thereby the alkalinized solution has a faster onset of action.

Dissociation of lignocaine (pKa = 7.9)

pH	Non-ionized (%)
3.45	< 5%
6.5	≈ 10%
7.4	≈ 24%

A solution with a pH more close to the pKa of the drug contains more drug in the non-ionized permeable form, hence a faster onset time.

Lignocaine Hydrochloride With Adrenaline

To prevent oxidation of adrenaline most commercially available local anaesthetic solutions containing adrenaline are supplied at a lower pH than their counterparts without adrenaline. In our study, the premixed lignocaine adrenaline solution used was supplied at a mean pH of approximately 3.45. Adrenaline counteracts the vasodilating effects of local anaesthetics and prolongs postoperative analgesia with lignocaine.

HYALURONIDASE

The discovery of hyaluronidase dates back to 1949 when Atkinson reported that larger injections of local anaesthetic for cataract surgery were feasible with hyaluronidase.

Hyaluronidase in an enzyme which deploymerizes the mucopolysaccharide hyaluronic acid, a component of the mucoprotein ground substance or tissue cement of the tissue spaces. It decreases the viscosity of the intercellular ground substance and helps quick dispersion of fluids infused subcutaneously. The deploymerizing effect is of short duration and reversible.

It is prepared from the testes and semen of mammals and purified so as to remove most of the inert material, sterilized and freeze dried.

Hyaluronidase is packed as a phosphate buffer and has maximal activity in the pH range 6.4 – 7.2; thus success increases with alkalinized lignocaine hyaluronidase mixture. Hyaluronidase also maintains anaesthetic solubility during alkalinization.

Due to its high activity and absence of untoward effects the quantity of hyaluronidase used is not critical. Usually 1 vial i.e. 1500 International Units (I.U.) is added to a 30 ml vial of lignocaine.

Hyaluronidase is virtually a non-toxic preparation. Allergy to hyaluronidase has been reported, but the report occurred many years ago when the process of purification was not at its current level.

CLASSIFICATION OF LOCAL ANAESTHETIC AGENT:

ESTERS

- Cocaine
- Benzocaine
- Procaine
- Amethocaine
- Chloroprocaine

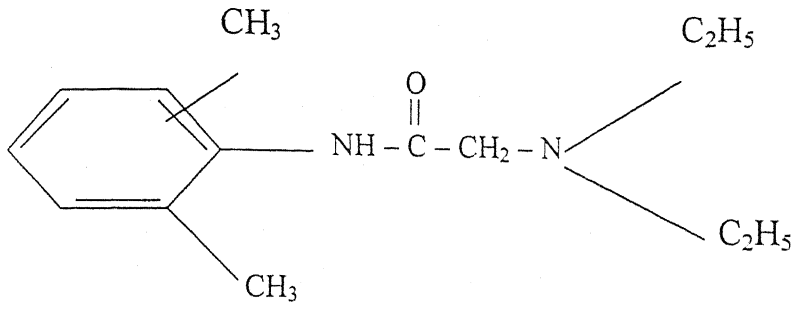
AMIDES

- Cinchocaine
- Lignocaine
- Mepivacaine
- Prilocaine
- Bupivacaine
- Etidocaine
- Ropivacaine

LIGNOCAINE

Lignocaine was synthesized in 1943 by Lafgren and Landquist and was first introduced in the clinical practice by Gordh in 1948. It is now one of the most widely used local anaesthetic agent. Its chemical name is Diethylamino – 2, 6 – aceto – xylidine.

It belongs to the Anilide group of amide local anaesthetics.



Structure of Lignocaine

Physiochemical Prpoperties:

Lignocaine hydrochloride is an odourless, white crystalline powder. Its partition co-efficient is 2.9, pKa is 7.9, molecular weight 234 and protein binding 64%.

Solubility:

It is freely soluble in water.

Stability:

Very stable, the stability of lignocaine is absolute within a wide range of temperature and pH.

Sterilization:

Vials containing lignocaine solution can be sterilized by boiling or autoclaving. Lignocaine crystals can be autoclaved for 6 hours or subjected to multiple autoclaving without loss of potency.

Absorption, Metabolism and Excretion:

Lignocaine is absorbed rapidly from the gastrointestinal and respiratory tracts even after parentral administration.

Although it is effective when used without any vasoconstrictor, in the presence of epinephrine the rate of absorption and toxicity is decreased, and the duration of action is usually prolonged.

The highest concentration of the drug is found in kidney after systemic absorption. Appreciable levels are found in lungs, spleen, heart and brain, low levels are found in the liver.

It has a high affinity for the fatty tissues. It has a half life of 1.6 hours. Most of the drug is metabolized by biotransformation into free and conjugated phenol. The ring structure is hydroxylated. It is metabolized in the liver by the enzyme oxidase to monoethylglycine and xylidine. The latter compound retains significant local anaesthetic and toxic activity. In man about 75% xylidide is excreted in the urine as 4 – hydroxy 2 – 6 diethyl aniline and less than 3% is excreted unchanged in urine.

Anaesthetic Properties:

Lignocaine is useful for ophthalmic blocks. It is effective topically when instilled into the conjunctional sac. Lignocaine is commonly made up with adrenaline in an attempt to delay the rate of absorption from the site of injection by producing local vasoconstriction. Lignocaine 2% is commonly used for ophthalmic blocks.

Lignocaine has a fast onset, but short duration. Three ml of a 1% concentration placed 5 to 7 mm behind the hind surface of the globe at the opening of the muscle cone will usually provide dilatation

of the pupil indicating block of the ciliary nerves within 10or 15 seconds. Onset of corneal anaesthesia occurs within a minute, and a minor effect on motor activity of the extraocular muscles in 90% of patients, but a significant motor block in 10%; 1% lignocaine will last from 20 minutes to an hour.

2% lignocaine will block the ciliary ganglion in approximately the same period of time and provide complete block of the extraocular muscles in 5 to 10 minutes in 75% of patients and will last for 45 minutes to 2 hours; 4% lignocaine will produce complete akinesia in 5 minutes in 75% and in 90% by 10 minutes but produce little or so akinesia in the remaining 10% of patients and will last from 1 to 3 hours.

Duration is quite variable with lignocaine. It is not uncommon for 4% to wear off in 30 to 45 minutes in persons with high levels of anxiety; this effect is probably due to blood flow or some other phenomenon, as yet incompletely understood in anxious people.

Local anaesthesia tend to wear off much more rapidly in people who use excessive alcohol, nicotine and barbiturates. Epinephrine is essential to adequate blocks in such people. Epinephrine extends the analgesia and akinesia time of lignocaine hereby providing a much more pleasant post-operative course.

Dosages:

Basically it should be remembered that smallest dose producing desired result should be given. Dosage for debilitated and aged

patients should be appropriately reduced. The suggested maximum dose of lignocaine with adrenaline is 7mg/kg body weight and without adrenaline is 3 mg/kg body weight.

Systemic Effects:

a) **Effect on central nervous system** : Lignocaine causes initial sleepiness in many patients. It has also been used as an anticonvulsant in the treatment of status epilepticus.

b) **Effect on the cardiovascular System** : Lignocaine is a useful drug in the treatment of cardiac dysrrhythmias. It stabilizes membrane of damaged and excitable cells tending to suppress ectopic foci. In therapeutic doses it causes no consistent change in the heart rate and does not depress conduction in purkinje fibres. (Bigger J.T. and Heisenbulted RH 1969).

There is usually no myocardial depression, instead improvement in the cardiac output and blood pressure has been observed when used in cardiac dysrrhythmias (Harrison DC et al, 1963). The greatest value of lignocaine is in the acute treatment of ventricular dysrrhythmias after myocardial infarction or cardiac surgery.

c) **Neuromuscular function and ganglionic synapse** : Local anaesthetics also affect transmission at the neuromuscular junction. Similar effect occurs at autonomic ganglia. These

effects are due to the block of the ion channel of acetylcholine receptors. (Neher and Steinbach 1978).

LOCAL ANAESTHETIC TOXICITY

Toxic reactions are generally caused by –

1. Relative overdose
2. Accidental intravascular injection leading to high plasma concentration.
3. Susceptibility of the individuals.
4. Various predisposing factors like liver disease, extremes of ages, pyrexia, shock, renal disease.

SYSTEMIC TOXICITY

Local anaesthetic toxicity is a function of plasma free drug concentration and is influenced by the drug, the dose and the injection site. The spectrum of toxicity extends from mild and non-threatening to cardio-respiratory collapse and death.

The early symptoms of toxicity are numbness of the tongue and circumoral region. Light headedness and tinnitus are encountered most frequently in patients on IV antiarrhythmic therapy. They appear at plasma lignocaine concentration of about 5 μg/ml. Further progression of toxic manifestations beyond mild central nervous system symptoms, like drowsiness, visual disturbances and muscular twitching occur at lignocaine concentration of 5 – 10 μg/ml. Above 10 μg/ml convulsions, coma and respiratory arrest are likely.

Profound CNS effect can occur with rapid injection of local anaesthetic into the head or neck because of retrograde flow into the brain from either arteries or veins. This bizarre, potentially lethal complication can only be prevented by slow injection.

Prevention and Management of Systemic Toxicity:

Prevention of local anaesthetic toxicity is a matter of minimizing blood concentration. Reducing blood concentration can be accomplished by slow injection, slow pick-up of anaesthetic from the tissue in which it has been deposited, and avoiding intravascular injection of the local anaesthetic drug.

High injection rate in an orbital vein can cause retrograde flow back into the brain with onset of convulsions, even though the concentration measured in the venous blood may be inconsequential. The actual concentration in the brain will be the major determinant.

Local anaesthetic injected in the sheath of the optic nerve can move subdurally or in the subarachnoid space along the optic chiasm into the subarachnoid space of the other eye or into the midbrain causing apnea, sympathetic blockade, or vagal blockade with varying cardiovascular effects. Brainstem anaesthesia is thus induced. However, this is not the only route by which brainstem anaesthesia can happen. Transfer across the intact dura, and hydraulic dissection along the dural cleavage zone of the attachment of the dura to the skull at the orbital apex are other mechanisms. Zahl has reported the latter for peribulbar anaesthesia.

ALLERGY

The treatment of acute allergic response is a major emergency. It is fortunate that allergy to the amide local anaesthetics is an extremely rare event.

Many so called allergic reactions to these drugs are reactions to their additives and preservatives and not to the local anaesthetics – methylparaben, a preservative, and sodium metabisulphite, an antioxidant, are the most common offender.

Reaction to ester drugs are more common.

APPLIED ANATOMY OF THE ORBIT

The orbit is a four-sided pyramid with its base pointing anteriorly and its apex posteromedially. The medial walls of the right and left orbits are parallel to each other. The mean distance from the inferior orbital margin to the apex is 55 mm. This has important implications when injections are made into the orbit. The deeper the injections, the narrower is the space, and the greater the chance of causing damage to the structures within. The inferotemparal quadrant is relatively avascular and is probably the safest approach for orbital injections.

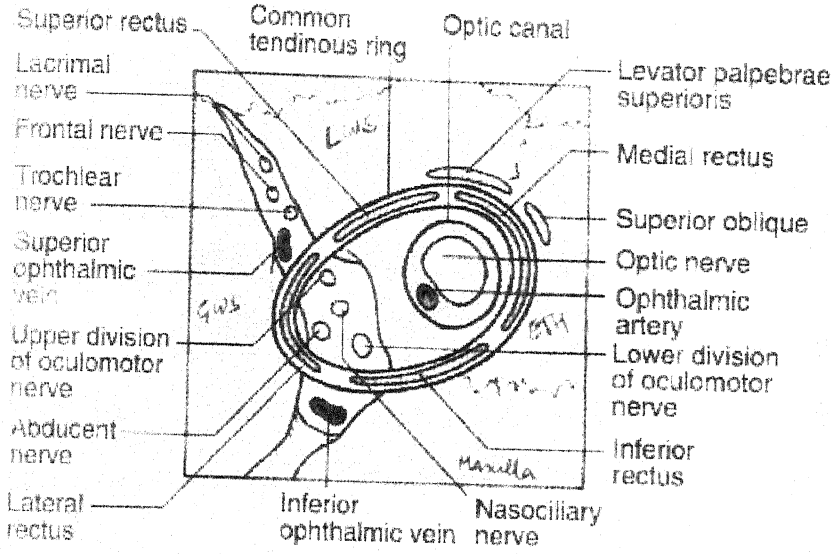


Fig. 1 The right superior orbital fissure

(Batterbury & Bowling - 1999)

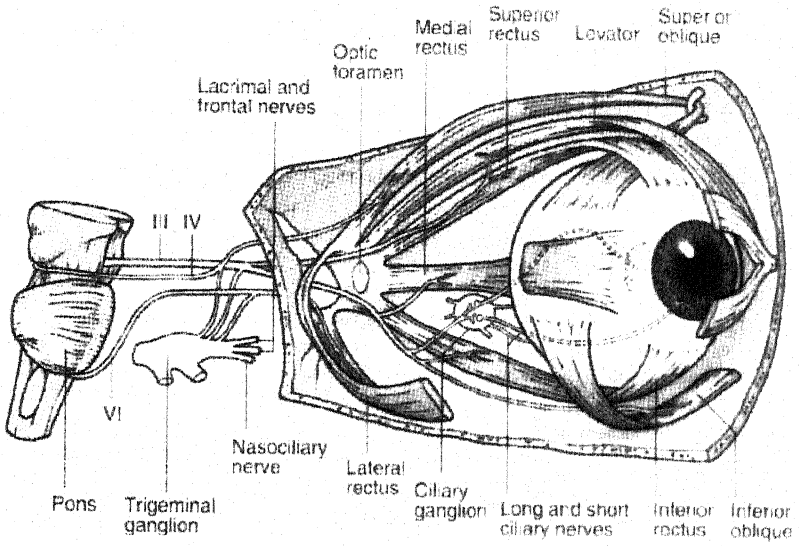


Fig. 2 The nerves and muscles of the orbit

(Batterbury & Bowling - 1999)

Squeezing and closing of the eyelids are controlled by the zygomatic branch of the facial nerve (VII), which supplies the motor innervation to the orbicularis oculi muscle. This nerve emerges from the foramen spinosum at the base of the skull, anterior to the mastoid and behind the earlobe. It passes through the parotid gland before crossing the condyle of the mandible, then passes superficial to the zygoma and malar bone before its terminal fibres ramify to supply the deep surface of the orbicularis oculi. The facial nerve also supplies secretomotor parasympathetic fibres to the lacrimal glands, and glands of the nasal and palatine mucosa.

Movement of the globe is controlled by the six extraocular muscles. The motor nerves which control these muscles emerge from the skull through the superior orbital fissure. The common tendinous ring forms the fibrous origin of the four rectus muscles at the apex of the orbital cone. The trochlear nerve (IV) emerges through the superior orbital fissure outside the common tendinous ring and supplies the superior oblique muscle. All the other motor nerves to the extraocular muscles pass inside the common tendinous ring and are situated inside the cone. The ophthalmic division of the oculomotor nerve (III) divides into superior and inferior branches before emerging from the superior orbital fissure. The superior branch supplies the superior rectus and the levator palpebrae superioris muscles. The inferior branch divides into three to supply the medial rectus, the inferior rectus and the inferior oblique muscles. The abducent nerve (VI) emerges from the superior orbital fissure beneath

the inferior branch of the oculomotor nerve to supply the lateral rectus muscle (Figure 1).

Sensation to the eyeball is supplied through the ophthalmic division of the trigeminal nerve (V). Just before entering the orbit, it divides into three branches : lacrimal, frontal and nasociliary. The nasociliary nerve is sensory to the entire eyeball. It emerges through the superior orbital fissure between the superior and inferior branches of the oculomotor nerve and passes through the common tendinous ring. Two long ciliary nerve give branches to the ciliary ganglion and, with the short ciliary nerves, transmit sensation from the cornea, iris and ciliary muscle. Some sensation from the lateral conjunctiva is transmited through the lacrimal nerve and from the upper palpebral conjunctiva via the frontal nerve. Both nerve are outside the cone (Figure 2).

The cone is the area between the four rectus muscles and the posterior surface of the globe. The muscles arise from a fibrous ring which bridges over the superior orbital fissure. Through this common tendinous ring pass the optic nerve, the ophthalmic artery, the two divisions of the oculomotor nerve, the nasociliary nerve and the abducent nerve. The superior and inferior ophthalmic veins may also pass through the ring. Tenon's capsule or bulbar fascia is a thin membrane that envelops the eyeball from the optic nerve to the sclerocorneal junction, separating it from the orbital fat and forming a socket in which it moves. The sheaths of the rectus muscles interconnect in the perimysium in a complex and variable manner and form the walls of the cone.

ANAESTHESIA TECHNIQUES FOR INTRAOCULAR SURGERY

Ophthalmic regional anaesthesia should provide conditions appropriate for the surgeon's needs and planned surgery.

Topical anaesthesia with 1% tetracaine, 0.4% oxybuprocaine eyedrops or other topical anaesthetic may be used for minor surgery to the conjunctiva if akinesia of the globe is not necessary.

Many different techniques and ingredients may be used to achieve the aims of akinesia, analgesia and a soft eyeball.

Three different methods are practiced:

- Extraconal (peribulbar)
- Intraconal (retrobulbar)
- Sub-Tenon's anaesthesia

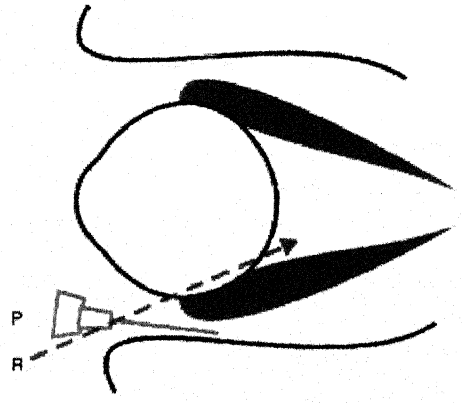


Fig 3 : Techniques for ocular anaesthesia : P = Peribulbar R = Retrobulbar

Intraconal anaesthesia places the injectate in the fatty compartment which surrounds the nerve to be blocked, whereas extraconal techniques rely on variable diffusion across connective tissue septa (Fig 3). Extraconal techniques were introduced more

recently in the expectation that the incidence of complications would be reduced. Sub-Tenon's injections involve a minor surgical procedure, and although avoiding some of the complication of the two other techniques, have their own problems.

All orbital blocks should be performed with the patient looking straight ahead in the primary gaze position. This ensures that the optic nerve is slack and out of the direct line of approaching needles.

The gauge of the needle should be the finest that can be used comfortably. In practice, this would be a 24 or 27 gauge needle, as finer needles are difficult to manipulate and larger needles may cause more pain and damage. Sharp needles are used because blunt needles are painful to insert and cause vasovagal syncope.

Following orbital injection, gentle digital pressure and massage help to dispense the anaesthetic agent and reduce IOP.

Extraconal (Peribulbar) Anaesthesia:

The techniques rely on the placement of relatively large volumes and high concentrations of local anaesthetic outside the cone. The anaesthetic mixture takes time to diffuse through the connective tissue layers of the cone. Spread of the anaesthetic superficially ensures that the terminal fibres of the facial nerve are blocked as they enter the orbicularis oculi. Most peribulbar methods require two initial injections. The volume injected depends on the shape of the orbit. The infertemporal injection should be made to a depth of no more than 30 mm from the infraorbital margin. The safest sites for

injection are in the inferotemporal quadrant and just mediall to the medial canthus. The superonsal quadrant should be avoided, as injection at this site may damage the trochlear apparatus or cause haemorrhage.

COMPLICATIONS OF LOCAL ANAESTHESIA

Haemorrhage

This is a serious complication of both intraconal and extraconal injection with a frequency between 0.1 and 3%. Haemorrhage may be either arterial or venous in origin and may be concealed or revealed. Extravasation of blood into the periorbital tissues increased the tissue volume and pressure. This is transmitted to the globe, raising the intraocular tension and creating difficult and dangerous conditions for intraocular surgery.

Prevention of Haemorrhage

Patients with hypertension are more likely to bleed and optimal control of arterial pressure should be achieved before surgery is attempted. The fewer injections that are made into the orbit, the less is the chance of damaging a blood vessel. Cutting and slicing movements at the needle tip should be avoided. Fine needles are less traumatic than thicker ones. Deep intraorbital injections are more likely to cause haemorrhage than are shallow injections. The inferotemporal quadrant has fewer blood vessels and is less hazardous. The addition of epinephrine to the injectate may reduce the incidence of haemorrhage. It is advisable to apply firm digital pressure to the

orbit as soon as the needle is withdrawn after an intraorbital injection, as this reduces any tendency to ooze.

Central Spread :

Mechanism

The cerebral dura mater provides a tubular sheath for the optic nerve as it passes through the optic foramen. This sheath fuses to the epineurium of the optic nerve and is continuous with the sclera, providing a potential conduit for local anaesthetic to pass subdurally to the brain. Central spread occurs if the needle tip has perforated the optic nerve sheath and injection is made. Even a tiny volume injected under the optic nerve sheath may pass to the central nervous system and/or cross the optic chiasma to the opposite eye and may cause life threatening sequelae. The time of onset of symptoms is variable, but any major sequelae develop usually in the first 15 minutes after the injection. It is therefore advisable that the patients face is not covered up on the operating table for at least this interval after the block has been inserted.

Signs and Symptoms of Central Spread:

The symptomatology of central spread is varied and depends upon which part of the central nervous system is affected by the local anaesthetic. As a result of the anatomical proximity of the optic nerve to the midbrain it is usual for this area to be involved. A range of different signs and symptoms has been described, involving the cardiovascular and respiratory systems, temperature regulation,

vomiting, temporary hemiplegia, aphasia and generalized convulsions. Palsy of the contralateral oculomotor and trochlear nerves with amaurosis is pathognomonic of CNS spread and should be sought in any patient whose response to questions following block are not as crisp as they were beforehand.

Treatment of Central Spread:

The treatment is symptomatic throughout the duration of effect of the local anaesthetic drug. With longer acting local anaesthetic agents, treatment must be required for 60 – 90 minutes. The patient must be monitored intensively.

Prevention of Central Spread:

Intraconal or extraconal injections should always be made with the patient looking strength ahead in the primary gaze position. The optic nerve is then slack and out of the way of the advancing needle. If the needle encounters the optic nerve in this position, it is unlikely to damage or perforate its sheath, as slackness in the structure allows the nerve to be pushed aside. If the eyeball is directed away from the primary gaze position in any other extreme direction, the optic nerve is stretched; the nerve cannot be easily pushed aside.

Puncture of the eyeball

Global puncture is a serious complication of local anaesthesia for eye surgery. It has been reported following both intraconal and extraconal injections.

Puncture of the eyeball is most likely to occur in patients with high myopia, previous retinal banding, posterior staphyloma or a deep sunken eye with a narrow orbit.

Global puncture is often a double puncture of the posterior segment of the eyeball. Puncture is usually recognized at the time of surgery and presents as an exceptionally soft eye. Timely management of posterior segment injury is a must because the needle track through the vitreous will eventually form a band of scar tissue. If this is not excised, it contracts and detaches the retina, sometimes causing sudden total blindness in the affected eye.

Optic Nerve Damage:

Fortunately, this is a rare complication which results from obstruction of the central retinal artery. This artery is the first and smallest branch of the ophthalmic artery, arising from the vessel as it lies below the optic nerve. It runs for a short distance within the dural sheath of the optic nerve and about 35mm from the orbital margin, pierces the nerve and runs forward in the centre of the nerve to the retina. Damage to the artery may cause bleeding into the confined space of the optic nerve sheath, compressing and obstructing blood flow. If the complication is recognized soon enough, it maybe possible to perform surgical decompression of the optic nerve.

Myopathy of the Extraocular Muscles:

The inadvertent injection of a long acting local anaesthetic into any extraocular muscle body may result in prolonged weakness of the

muscle. An injection site some distance away from these muscles should be selected.

Vasovagal Syncope:

This is more like to occur in young and anxious patients when eye blocks are administered. Painful injection with a blunt Atkinson needle may cause this response. It is important that a vein is cannulated before any block is given. Treatment is symptomatic and should include administration of oxygen, intravenous injection of an anticholinergic agent and appropriate positioning. Differentiation from central spread should be made by testing vision and extraocular movements in the opposite eye.

MATERIAL AND METHODS

MATERIAL AND METHODS

The present study was undertaken in the Department of Ophthalmology, M.L.B. Medical College and Hospital, Jhansi during the period of October 2001 to Janaury 2003.

SELECTION OF CASES

The cases for this study were selected from the indoor patients of M.L.B. Medical College and Hospital, Jhansi. The patients selected were those requiring surgery for age – related cataract. ***(Age - related cataract was taken as lenticular opacities occurring in people 40 years and above without any evident cause).*** All cases were subjected to routine pre-operative evaluation.

The exclusion criteria were –

- Patients with documented allergies to lignocaine hydrochloride.
- Patients with profound cognitive impairments who were unable to give informed consent.
- Patients with uncontrolled diabetes and hypertension.
- Patients with raised IOP.

STUDY DESIGN

After a written informed consent the 210 patients included in the study were randomly divided into 3 groups of 70 each.

Group 1 Subjects received 8 ml of 2% lignocaine with adrenaline + 50 IU/ml Hyaluronidase (pH = 3.45)

Group 2 Subjects received 8 ml of an alkalinized solution of 2% lignocaine with adrenaline (pH = 6.5)

Group 3 Subjects received an alkalinized solution of 2% lignocaine with adrenaline + 50 IU/ml Hyaluronidase (pH = 6.5)

Each solution was freshly prepared prior to injection and the pH determined by a digital pH meter. Alkalinization was done by adding the required amount of sodium bicarbonate 7.5% (wt/vol) to 2% lignocaine hydrochloride with 1:200000 adrenaline solution.

All blocks were performed by one person, who was unaware of the nature of mixture selected for use.

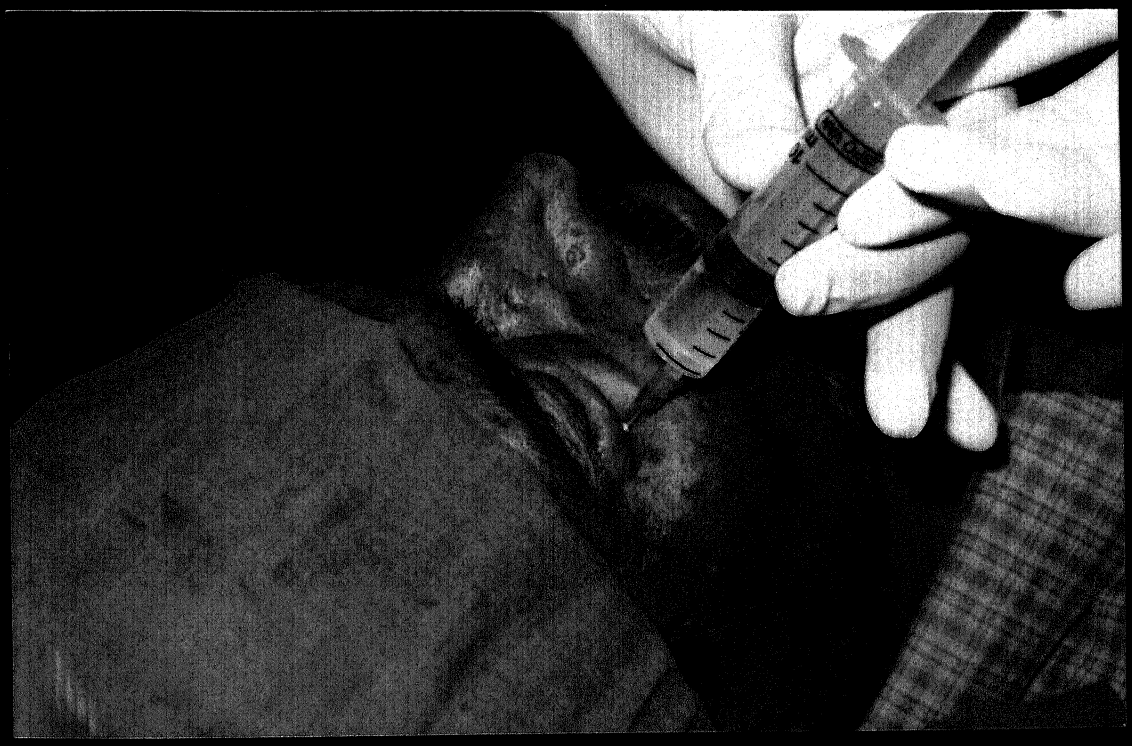
Technique of Peribulbar Block:

With the eye in primary gaze superior and inferior injections of 5 ml and 3 ml respectively are given with a 1 inch, 24 gauge needle.

The inferior injection was given at the junction of the outer one third and inner two thirds of the lower orbital rim. The needle was directed away from the eye and towards the floor of the orbit with the eye in primary gaze. The superior injection was given in the superonasal quadrant, nearer to the medial canthus. Both injections were placed outside the muscle cone. After the injections, each patient received digital massage over the eyelids with gauze, all by one person only. Extraocular muscle movement was evaluated in each quadrant at 2 minute intervals for 15 minutes. A block was considered

REQUIREMENTS FOR PERIBULBAR BLOCK

GIVING THE PERIBULBAR BLOCK



satisfactory when akinesia occurred. Supplement injection in the form of retro-bulbar block was given with the same mixture after 15 minutes in cases with persistent eye movement.

Parameters assessed include –

- **Time to onset of akinesia:**

  It is the time taken for total/adequate akinesia. This is measured from the time of injection till total or adequate (movement of less than 1 mm in any direction) akinesia occurs, to proceed for safe surgery. This includes akinesia of eyeball as well as of the lids. Following the peribulbar injection akinesia of the eyelids and globe is checked for every 2 minutes for 15 minutes. This is done by asking the patient to move the eyeball in various directions and to squeeze the eyes voluntarily.

- **Residual movements:**

  At the end of 15 minutes each patient was asked to move the eyeball in all the directions and if movement is there in any particular direction it is noted.

- **Supplementary Anaesthesia required:**

  If there was significant movement of the eyeball at the end of 15 minutes, the peribulbar block was supplemented with a retro-bulbar injection with the same mixture. Such cases were noted.

- **Duration of Akinesia and Anaesthesia:**

  This is taken from the time of achievement of akinesia and anaesthesia till the completion of surgery or wearing-off of

anaesthesia or akinesia whichever is earlier of the two. The sign of wearing-off of akinesia is so much movement of the eyeball in any direction that it required supplemental injection and sign of wearing-off of anaesthesia is taken by the complaining of pain by the patient.

❖ **Post Injection Thrust During Surgery:**

(Subjective to the Surgeon)

Thrust is the pressure applied by the vitreous as well as retro-orbital tissues on the anterior chamber of the eye when the eye has been opened for surgery. This is not synonymous with intraocular pressure since it has been seen that even though intraocular pressure may be low preoperatively, on opening the anterior chamber there is thrust of the vitreous. This is seen when too much (usually 10 ml) of anaesthetic solution has been deposited in the periorbital space or there is retrobulbar haemorrhage. Thrust was recorded as no thrust, minimal, moderate and a substantial thrust leading to difficulty in operation.

❖ **Conjunctival Chemosis:**

This is more commonly observed after peribulbar injection due to more solution deposited. This was recorded as no chemosis, mild chemosis, i.e. chemosis in one quadrant, moderate = 2 quadrants, severe = >2 quadrants.

❖ **Lid Edema:**

Edema of the lids following the peribulbar injection was taken note of as this may result in difficulty in opening of the palpebral aperture and consequently a pressure on the eye ball.

❖ **Pulse and BP:**

This were monitored pre-operatively and 10 minutes after injection of the peribulbar block.

❖ **Post-operative Subjective Onset of Pain:**

This is a subjective feeling and is assessed by asking the patient at 30 minute intervals for the initial 2 hours following surgery, whether he feels pain or not.

OBSERVATIONS AND RESULTS

OBSERVATIONS

TABLE No. 1
Demographical Features of the Population

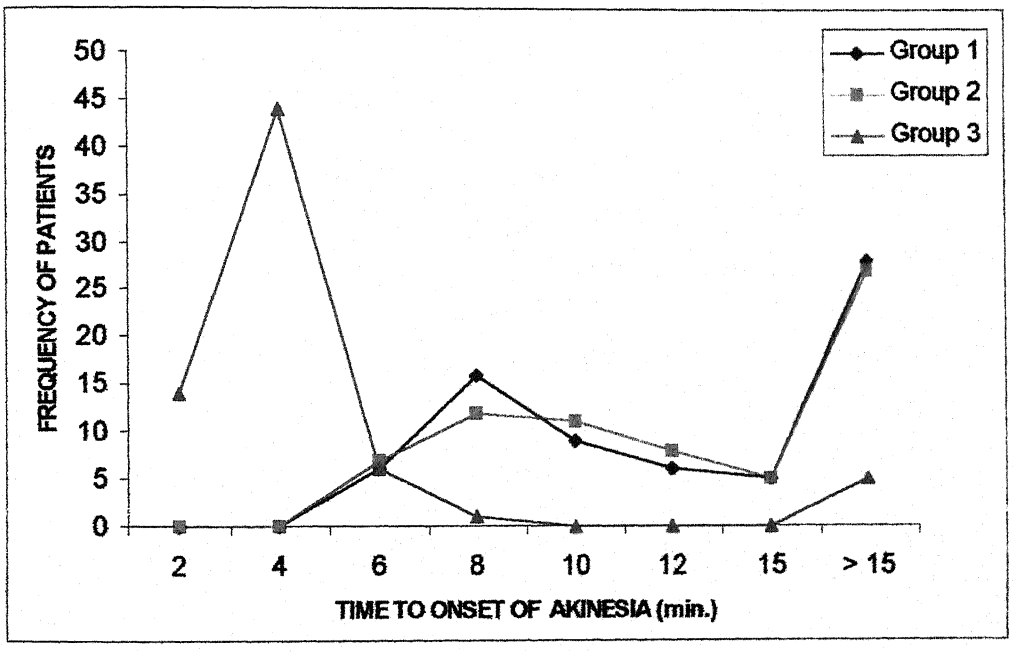
Particulars	*Group 1*		*Group 2*		*Group 3*	
Sex	*M*	*F*	*M*	*F*	*M*	*F*
Number	36	34	39	31	37	33
Age Group	40 – 75	45 - 82	45 - 75	45 - 75	47 - 80	40 - 75
Age Mode	60	60	60	60	60	60
Age Mean	61.13	60.55	62.69	60.09	61.97	58.84
Sex Ratio M/F	1.1		1.3		1.1	

It is evident from the above table that most of the cases were between 45 – 75 years. The male female ratio was 1.1 in Group 1 and 3, and 1.3 in Group 2.

TABLE No. II

Time to onset of Akinesia (Minutes)

Observed Frequency			
Time Minute	***Group 1***	***Group 2***	***Group 3***
2	0	0	14
4	0	0	44
6	6	7	6
8	16	12	1
10	9	11	0
12	6	8	0
15	5	5	0
>15	28	27	5
Total	***70***	***70***	***70***



Curve

As seen in the frequency distribution curve 65 of the 70 patients in Group 3 had a time to onset of akinesia within 8 minutes. This is in contrast to 42 patients in Group 1 and 43 in Group 2 who had a time to onset of akinesia by 15 minutes.

TABLE No. III

TOTAL AKINESIA AT THE END OF 15 MINUTES

Post Injuc - tion thrust	Observed frequency			Total	Expected frequency		
	Group-1	Group 2	Group 3		Group-1	Group 2	Group 3
Yes	42	40	65	147	49.0	49.0	49.0
No	28	30	5	63	21.0	21.0	21.0
Total	70	70	70	210	70	70	70

Statistics **CHI^ = 26.056**

d.f. = 2

d.f	2 Probability	
	1%	5%
2	9.21	5.99
1	6.63	3.84

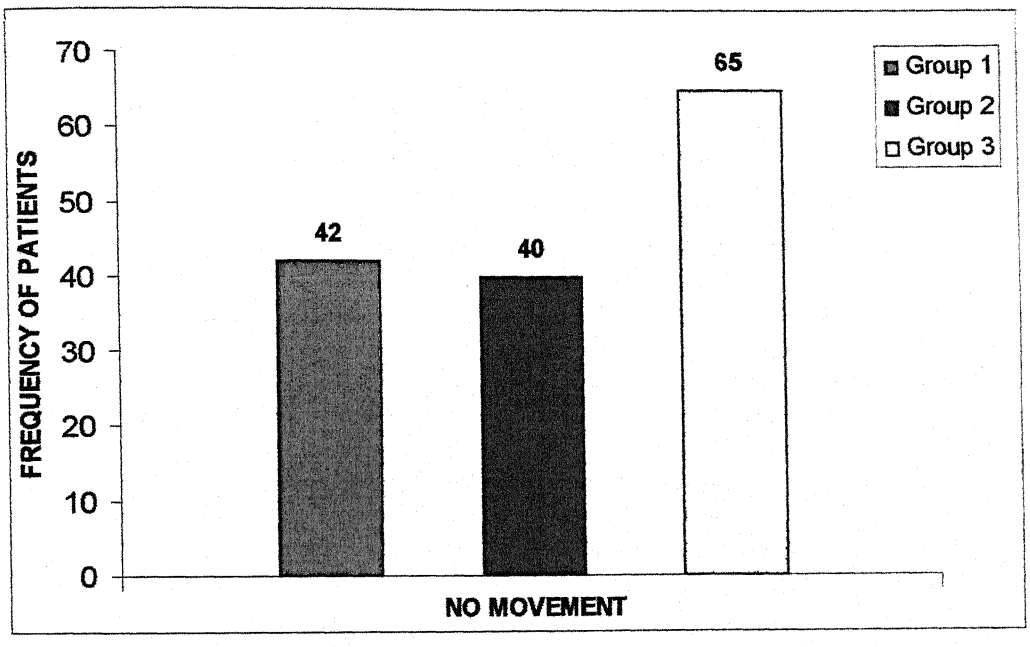
Inference: The difference between groups in highly significant

To ascertain which group differ significantly from each other.

The Chi^2 test is applied between combination of two groups.

Group	d.f	Chi^2	Inference
1 & 2	1	0.03	The difference between groups is not significant
1 & 3	1	19.19	The difference between groups is highly significant
2 & 3	1	21.94	The difference between groups is highly significant

Bar Diagram Showing Cases with No Movement



42 patients in group 1, 40 in group 2 and 65 in group 3 showed complete akinesia at end of 15 minutes. The Chi^ 2 test shows no significant difference between group 1 and 2, whereas a significant difference exists between group 1 & 3 and 2 & 3 at 1% level of significance.

TABLE No. IV

REBLOCK REQUIRED (YES / NO)

Reblock required	Observed frequency			Total	Expected frequency		
	Group-1	Group 2	Group 3		Group-1	Group 2	Group 3
Yes	24	25	5	54	18	18	18
No	46	45	65	156	52	52	52
Total	70	70	70	210	70	70	70

Statistics **CHI^ = 26.056**

d.f. = 2

d.f	2 Probability		
	1%	5%	10%
2.00	9.21	5.99	4.61
1.00	6.63	3.84	

Inference: The difference between groups in highly significant,

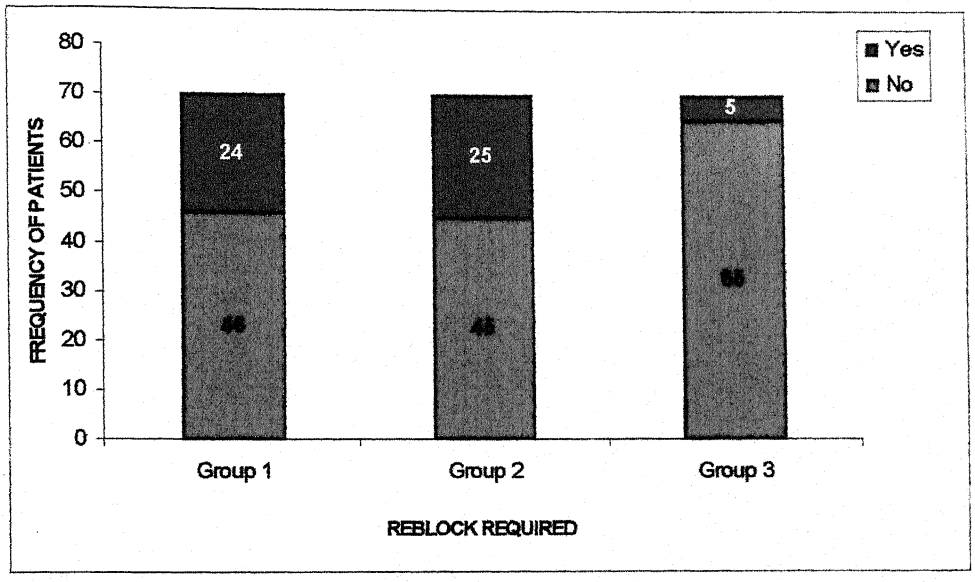
at less than 1% level of significance

To ascertain which group differ significantly from each other.

The Chi^2 test is applied between combination of two groups.

Group	d.f	Chi^2	Inference
1 & 2	1	0.03	Group are not significantly different
1 & 3	1	15.58	The difference between groups is highly significant (<1%)
2 & 3	1	11.44	The difference between groups is highly significant (<1%)

Bar Diagram Showing No. of Patients Requiring Reblock



24 patients in group 1 and 25 patients in group 2 required supplementary anaesthesia in the form of retrobulbar block in sharp contrast to only 5 patients in group 3 requiring reblock.

TABLE No. V

Post Injection Thrust (Yes/No)

Post-injuction thrust	Observed frequency			Total	Expected frequency		
	Group-1	Group 2	Group 3		Group-1	Group 2	Group 3
Yes	3	3	0	6	2.0	2.0	2.0
No	67	67	70	204	68.0	68.0	68.0
Total	70	70	70	210	70	70	70

Statistics **CHI^ = 3.09**

d.f. = 2

d.f	2 Probability		
	1%	5%	10%
2.00	9.21	5.99	4.61
1.00	6.63	3.84	

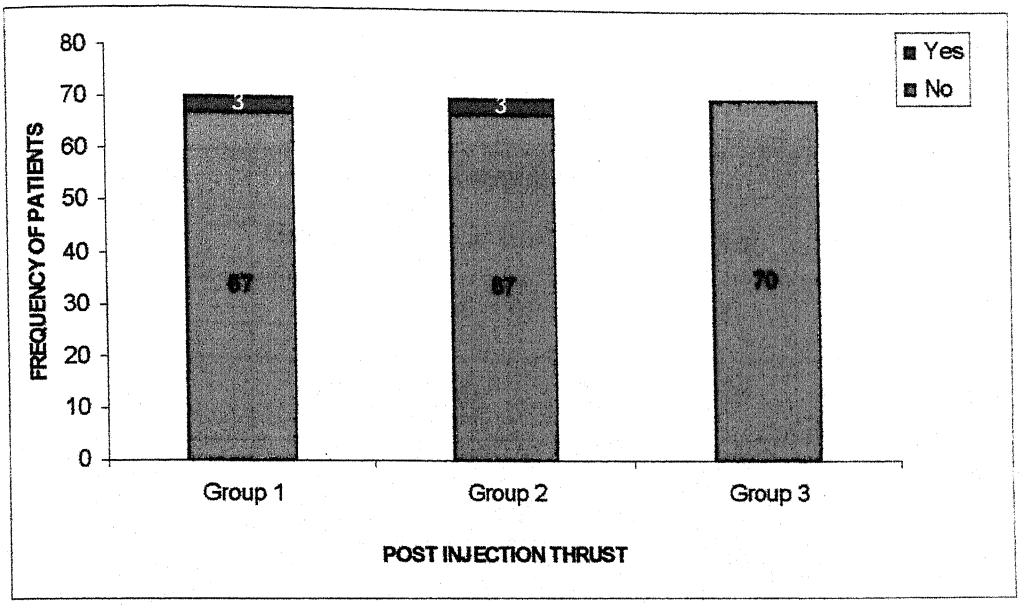
Inference: The difference between groups is not significant,

To ascertain which group differ significantly from each other.

The Chi^2 test is applied between combination of two groups.

Group	d.f	Chi^2	Inference	
1 & 2	1	0.17	The difference between groups is	Not significant
1 & 3	1	1.36	The difference between groups is	Not significant
2 & 3	1	11.44	The difference between groups is	Not significant

Bar Diagram Showing Cases with Post Injection Thrust



As seen in the above diagram 3 cases in group 1 and 2 showed post injection thrust whereas none of the cases in group 3 showed any post injection thrust. The difference between the groups is not significant.

TABLE No. VI

CONJUNCTIVAL CHEMOSIS (YES / NO)

Conjunctival Chemosis	Observed frequency			Total	Expected frequency		
	Group-1	Group 2	Group 3		Group-1	Group 2	Group 3
Yes	0	4	0	4	1.3	1.3	1.3
No	70	66	70	206	68.7	68.7	68.7
Total	70	70	70	210	70	70	70

Statistics

CHI^= 8.16

d.f. = 2

d.f	2 Probability			
	1%	5%	10%	20%
2.00	9.21	5.99	4.61	3.22
1.00	6.63	3.84		

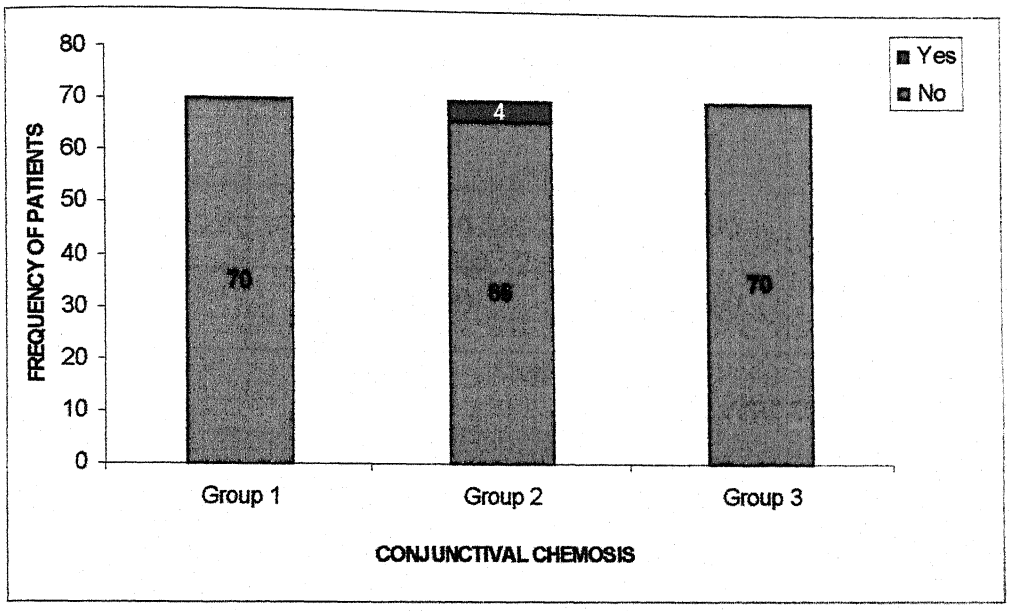
Inference: The groups are significantly different at 5% level of significance

To ascertain which group differ significantly from each other.

The Chi^2 test is applied between combination of two groups.

Group	d.f	Chi^2	Inference
1 & 2	1	4.12	Groups are significantly different at 5% level of significance
2 & 3	1	4.12	Groups are significantly different at 5% level of significance
1 & 3	1		No difference

Bar Diagram Showing Cases with Conjunctival Chemosis



4 patients in Group 2 had conjunctional chemosis whereas none of the patients in Group 1 & 3 had any chemosis.

TABLE No. VII

LID EDEMA

Lid Edema	Observed frequency			Total	Expected frequency		
	Group-1	Group 2	Group 3		Group-1	Group 2	Group 3
Yes	0	4	0	4	1.3	1.3	1.3
No	70	66	70	206	68.7	68.7	68.7
Total	70	70	70	210	70	70	70

Statistics

CHI^= 8.16

d.f. = 2

d.f	2 Probability			
	1%	5%	10%	20%
2.00	9.21	5.99	4.61	3.22
1.00	6.63	3.84		

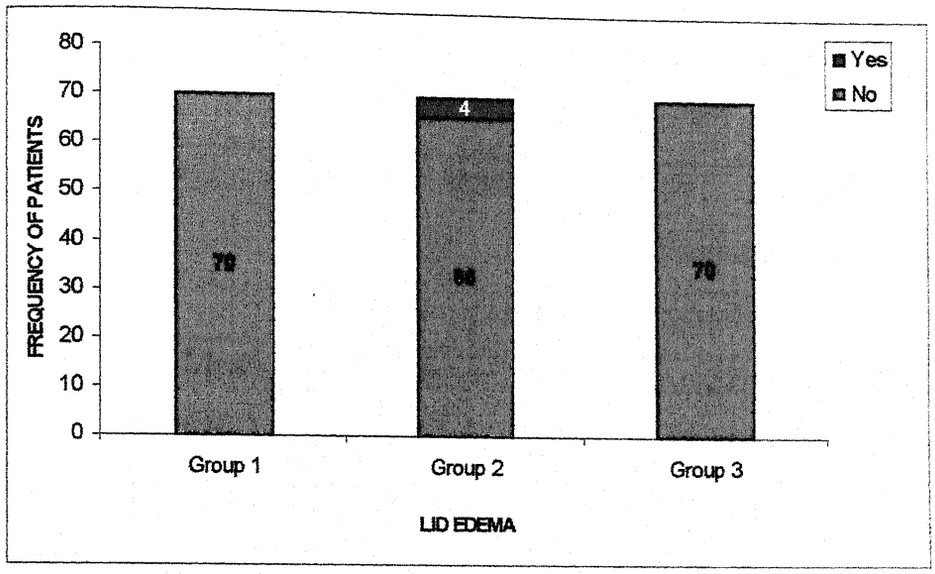
Inference: The groups are significantly different at 5% level of significance

To ascertain which group differ significantly from each other.

The Chi^2 test is applied between combination of two groups.

Group	d.f	Chi^2	Inference
1 & 2	1	4.12	Group are significantly different at 5% level of significance
2 & 3	1	4.12	Group are significantly different at 5% level of significance
1 & 3	1		No difference

Bar Diagram Showing Cases with Lid Edema



4 Patients in group 2 developed lid edema. One of these patients was postponed due to the tight palpebral aperture. In the other 3 patients surgery proceeded successfully expect that the surgeon faced problems due to vitreous thrust, 3 patients in group 1 also had vitreous thrust, but the results of surgery were good in all 6 cases.

TABLE No. VIII

Changes in the Mean Systolic and Diastolic Blood Pressure (mmHg) in different study groups.

Group		Pre-Operative		10 minute after Peribulbar injection	
		Systolic	Diastolic	Systolic	Diastolic
Group I (n=70)	Mean ± S.D.	127.5 ±15.0	79.3 ±8.6	127.5 ±14.0	78.1 ±8.4
Group II (n=70)	Mean ± S.D.	125.2 ±12.2	77.4 ±6.6	125.3 ±11.7	77.4 ±6.7
Group I (n=70)	Mean ± S.D.	129.7 ±16.1	77.9 ±7.1	128.5 ±14.3	78.0 ±6.9

P>0.05

The above table shows no significant change in the mean systolic and diastolic blood pressure from their preoperative values at 10 minutes post operatively in any of the three groups.

TABLE No. IX

Changes in the Mean Pulse Rate (beats /min) in different study groups

Group		Pre-Operative	10 minute after Peribulbar injection
Group I	Mean	79.3	79.3
(n=70)	± S.D.	±7.1	±6.5
Group II	Mean	78.8	78.9
(n=70)	± S.D.	±7.3	±6.9
Group I	Mean	79.2	80.0
(n=70)	± S.D.	±9.0	±8.6

P>0.05

The above table indicates that the pre-operative pulse rate among the groups were linear and within normal range. After 10 minutes of the peribulbar injection of the local anaesthetic drug, no significant rise or fall in pulse rate was noted in any of the groups.

TABLE No. X

Duration of Surgery

(in minutes)

Group		Duration
Group 1 (n=70)	Mean	18.47143
	± S.D.	±2.32
Group 2 (n=70)	Mean	18.55714
	± S.D.	±2.57
Group 3 (n=70)	Mean	18.00
	± S.D.	± 2.25

P>0.05

The above table shows that the mean duration of surgery among the three groups is comparable at p>0.05.

DISCUSSION

DISCUSSION

The present study is an attempt to compare the relative efficacy of alkalinization and/or hyaluronidase with 2% lignocaine hydrochloride plus adrenaline, in peribulbar block for routine cataract surgery.

Modification of local anaesthetic by the addition of agents such as hyaluronidase and sodium bicarbonate has been practiced for some time now. Fernando and Jones (1991) studied the comparison between the effect of plain and alkalinized mixtures of lignocaine and bupivacaine for elective extradural caesarean section. Modification of a local anaesthetic is usually carried out, either, to speed the onset of bock i.e. by adding sodium bicarbonate or hyaluronidase or, for prolonging the duration of block i.e. by adding adrenaline. As yet there is no local anaesthetic available that combines reliable quick onset with prolonged action.

The present study was carried out on 210 healthy patients, between 40-82 years age scheduled for senile cataract surgery. These patients were randomly allocated into three groups of seventy each. pH of the groups was constituted by adding the required amount of 7.5% sodium bicarbonate solution. pH of Group-1 was kept at 3.45, Group-2 and Group-3 at 6.5 each.

The parameters recorded in each group are as follows :-

- Time to onset of akinesia
- Residual movements
- Supplementary anaesthesia required
- Duration of akinesia and anaesthesia
- Post – Injection Thrust
- Conjunctinal chemosis
- Lid edema
- Pulse, BP
- Post-operative subjective onset of pain

The demographic and operative data in all the groups was comparable. Most of the patients in each group were between the age of 45 to 75 years. All had acquired senile cataract. Male/Female ratio was 1.1 in Group-1 and 3, 1.3 in Group 2. All the patients underwent an identical procedure for routine cataract surgery i.e. ECCE with PC IOL implantation, all performed by one surgeon. The mean duration of surgery for each case was comparable in all the three groups; 18.47 $\pm$ 2.32 minutes for Group-1, 18.55 $\pm$ 2.57 minutes for Group-2 and 18.00 $\pm$ 2.25 minutes for Group-3 patients.

Time to onset of akinesia

It is the time taken from the time of giving the injection to the time of appreciable restriction of movements of the globe and loss of lid movements. Following the peribulbar injection this was checked

for every 2 minutes for 15 minutes. The patients was asked to move the eyeball in various directions and to squeeze the lids.

In this study, as seen in the frequency distribution curve on page 45, 65 out of 70 patients in Group 3 had a time to onset of akinesia within 8 minutes. This is in contrast to 42 patients in Group 1 and 43 in Group 2 who had a time to onset of akinesia by 15 minutes.

These results co-relate well with the findings of earlier studies which are as follows :

Zahl et al (1991) showed that pH adjusted lignocaine + bupivacaine had a faster onset of complete akinesia (7.0 ± 2 minutes) when compared with the other groups.

Roberts et al (1993) in their study on peribulbar anaesthesia with alkalinization and hyaluronidase demonstrated that the solution containing hyaluronidase and pH adjusted to 6.7 was the most effective.

Lewis et al (1992) while studying plain versus pH – adjusted bupivacaine for eye block noted a shortened onset time of peribulbar block but this was associated with excessive orbicularis muscle activity and thus a requirement for increased supplementation compared with plain solution.

Srinivasan et al (2000) in their study on sodium bicarbonate an alternative to hyaluronidase in ocular anaesthesia for cataract surgery concluded that 51.5% eyes achieved complete akinesia within 5

minutes in the bicarbonate group in comparison to 21.6% eyes attaining complete akinesia within 5 minutes in the hyaluronidase group. The mean time to onset of akinesia was 7.51 ± 5.89 minutes in the pH – adjusted group whereas it was 8.86 ± 3.82 minutes in the hyaluronidase group.

In the present work Group 1 patients who received an acidic injectate (pH = 3.45) of an 8ml solution of 2% lignocaine with adrenaline 1:200,000 + 50 IU/ml hyaluronidase had a higher onset time (47 out of 70 by 15 minutes) as compared to group 3 patients (65 out of 70 within 8 minutes). This may be because the volume of injectate being less than the volume of the periocular space, initially compartmentalizes where the endogenous buffering systems slowly neutralize this acidic solution. Also hyaluronidase is inactive at this pH; thus explaining for the prolonged onset time.

Group 2 patients who received on alkalinized injection (pH = 6.5) of 2% lignocaine with adrenaline 1:200000 also showed a higher onset time (43 out of 70 by 15 minutes). This result is against the pharmacokinetic theories of local anaesthetic solutions but can be explained according to the thermodynamic principles for weak bases i.e. an increase in temperature and pH (Kamaya et al) results in more of the less soluble neutral species. After the peribulbar injection the solution initially compartmentalizes and heating by the surrounding tissues results in more of the neutral species and precipitation. Consequently there is poor absorption, reduced efficacy, lid edema, chemosis and tightening of palpebral aperture.

Group 3 patients who received an alkalinized lignocaine hyaluronidase injectate had the shortest onset time (65 out of 70 within 8 minutes). This can be attributed, firstly to, hyaluronidase being an enzyme (protein), decreases the rate of crystal formation and subsequent precipitation. Also a combination of increased hyaluronidase activity and anaesthetic lipophilicity results in decreased compartmentalization and precipitation.

Supplementary Anaesthesia required

If there was movement (> 1 mm in any direction) of the eyeball at the end of 15 minutes, the peribulbar block was supplemented with a retro-bulbar injection with the same mixture.

In the present study only 5 out of 70 patients (0.71%) in Group 3 i.e. in the pH adjusted lignocaine hyaluronidase group required reblock in sharp contrast to 24 out of 70 (34.2%) in Group 1 and 25 out of 70 (35.7%) in Group 2 requiring the retrobulbar block.

These results co-relate well with –

Zahl et al (1991), who showed that 2 out of 20 patients in the pH adjusted group required supplemental injection against 4 out of 20 in the plain group at the end of 30 minutes. He found these results not to be significant by Fisher's exact analysis.

Roberts et al (1993) while comparing the effect of pH and the addition of hyaluronidase to a mixture of lidocaine and bupivacaine on the efficacy of peribulbar block found only 2 out of 20 patients

requiring reblock in the pH adjusted lidocaine bupivacaine hyaluronidase group (pH = 6.7) against 11 out of 20 requiring reblock in the plain lignocaine bupivacaine hyaluronidase group (pH = 5.0).

Srinivasan et al (2000) in their study found reblock rate to be 21.66% in the pH – adjusted group while it was 18.33% in the hyaluronidase group.

The results of this study do not co-relate with the findings of

Lewis et al (1992) according to whom the requirement for anaesthetic supplement at 20 minutes was 9 out of 26 in the plain group and 13 out of 24 in the pH adjusted group. According to him pH – adjusted bupivacaine shortened the onset time of peribulbar block but was associated with excessive orbicularis muscle activity and a requirement for increased supplementation compared with the plain solution.

Supplement injections add to the risk of complications with each prick and so defeat the very purpose of the peribulbar block. This can be avoided to the maximum with group 3 solution, whereas, the supplement injection rate increased in group 1 and group 2 thereby increasing the probability of complications.

Residual Movements

At the end of 15 minutes each patient was asked to move the eyeball in all directions and the remaining movement, if present was

noted. Total akinesia or movement of less than 1 mm in any direction is taken as adequate for safe surgery to proceed.

In our study success was 92.8% in group 3 patients (65 out of 70) who received an 8 ml injectate of an alkalinized solution of 2% lignocaine with adrenaline and 50 IU/ml hyaluronidase (pH = 6.5). This is in contrast to 60% patients in Group 1 (42 out of 70) and 57.1% in Group 2 (40 out of 70) who achieved total akinesia at the end of 15 minutes. In our study success was 92.8% in Group 3 patients (65 out of 70) who received an 8 ml injectate of an alkalinized solution of 2% lignocaine with adrenaline and 50 IU/ml hyaluronidase (pH =6.5). This is in contrast to 60% patients in Group 1 (42 out of 70) and 57.1% in group 2 (40 out of 70) who achieved total akinesia at the end of 15 minutes.

Most surgeons are content with small amounts of residual movements but complete akinesia is the ultimate requirement for safe and successful surgery.

In our study we observed that the last muscle to attain akinesia was the medial rectus, while the vertical movements were lost the earliest.

The above results are in accordance with : Roberts et al (1993) who demonstrated a 10% failure rate in the lidocaine bupivacaine hyaluronidase adjusted to pH 6.7 group in comparison to a 55% failure rate in the bupivacaine hyaluronidase group where pH was 5.0.

Srinivasan et al (2000) while comparing pH – adjustment with hyaluronidase concluded a success rate of 78.3% in the pH-adjusted group against 81.6% in the hyaluronidase group.

Duration of akinesia and anaesthesia

In the present study duration of akinesia and anaesthesia is taken from the time of achievement of akinesia till the completion of surgery or wearing-off of anaesthesia or akinesia, whichever is earlier of the two.

Mean duration of surgery for each case in Group-1 was 18.47 ± 2.32 minutes, Group-2 18.55 ± 2.57 minutes, Group-3 18.00 ± 2.25 minutes. None of the patients in any group complained of pain or discomfort during the whole surgical procedure and neither was any movement of the eyeball or the twitching of lids seen during this time.

Therefore we can conclude that alkalinization of lignocaine hydrochloride solution is as efficacious as the non-alkalinized solution concerning the quality of block.

Results of the present study are comparable with those of Zahl et al (1991), Lewis et al (1992) and Srinivasan et al (2000); all of whom have reported that there was no supplementary injections required once surgery had commenced and that all patients were comfortable during the procedure.

Post Injection Thrust (Subjective to the surgeon)

Thrust is the pressure applied by the vitreous as well as retro-orbital tissues on the anterior chamber of the eye when the eye has been opened for surgery. This is not synonymous with intraocular pressure since it has been seen that even though intraocular pressure may be low pre-operatively, on opening of the anterior chamber there is thrust of the vitreous. This is seen when too much of the anaesthetic solution has been deposited in the periorbital space or there is retrobulbar haemorrhage.

In our observation the post-injection thrust as experienced by the surgeon was minimal in 3 cases each in Group 1 and 2 out of the total 70 i.e. 4.2% while none of the cases in Group 3 had any thrust. The difference between the three groups is not significant.

None of the previous studies have reported any case of post-injection thrust with alkalinization.

Conjunctival Chemosis

Post-injection conjunctival chemosis occurs more commonly with peribulbar anaesthesia due to diffusion of anaesthetic solution into the subconjunctival space. This also indicates the success of the block and is a necessary evil for proper anaesthesia. However, it has been observed by us as well as by other authors that moderate amount of chemosis does not hamper surgery in any way.

In our results 4 patients out of the 70 in Group 2 had chemosis; 3 had mild chemosis i.e. in one quadrant only while 1 had moderate chemosis i.e. in 2 quadrants. This chemosis did not interfere in the

surgical procedure in any of the 4 cases and the results of surgery were good in all these 4 cases. None of the cases in Group 1 and 3 had any conjunctival chemosis. These results are significant at 5% level of confidence.

Thus we can conclude that alkalinization alone may lead to significant chemosis when compared with plain lignocaine hydrochloride or with hyaluronidase along with alkalinization.

Lid Edema

Edema of the lids following the peribulbar injection was taken note of as this may result in difficulty in opening of the palpebral aperture and consequently a pressure on the eyeball.

In the present study 4 patients in group 2 developed lid edema. One of these patients was postponed due to a tight palpebral aperture. In the other 3 patients surgery proceeded successfully expect that the surgeon faced minimal vitreous thrust. None of the cases in group 1 and 3 had any lid edema.

None of the previous studies have mentioned any lid edema in any of the cases. Srinivasan et al (2000) have reported no anaesthetic adverse effects such as lid edema, chemosis and congestion while comparing the efficacy of sodium bicarbonate with hyaluronidase.

Post-operative subjective onset of pain

This a subjective feeling and is assessed by asking the patient at 30 minute intervals for the initial 2 hours following surgery whether he feels pain or not.

None of the patients in any group felt pain so severe as to require supplement analgesia post-operatively which is a routine practice at our institution.

Systemic Safety Variables

There was no significant differences in the pulse rate, systolic and diastolic B.P. pre-block and 10 minutes post-block in any of the cases in any group. There was no untoward event during the surgery or post-operative period.

CONCLUSION

CONCLUSION

The conclusions drawn from a comparative study of the effect of 2% lignocaine hydrochloride with adrenaline ± hyaluronidase at 3 different pH in peribulbar block technique of ocular anaesthesia for cataract surgery are as follows :

1. Raising the pH of 2% lignocaine hydrochloride with adrenaline and hyaluronidase solution from 3.45 to 6.5 produced a definite reduction in the onset of akinesia.

2. Alkalinized lignocaine hydrochloride with adrenaline alone or lignocaine hydrochloride with adrenaline and hyaluronidase without alkalinization were not as effective as a solution containing alkalinized lignocaine hydrochloride with adrenaline and hyaluronidase.

3. The duration of bock was comparable in all 3 groups.

4. More cases achieved complete akinesia in the alkalinized lignocaine hydrochloride with adrenaline + hyaluronidase group.

5. Alkalinized lignocaine hydrochloride with adrenaline + hyaluronidase was more efficacious than the other two solutions. Therefore need for supplement injections was reduced in this group.

6. Vertical movements were the first to go: medial movement was the last to go.

7. Alkalinized lignocaine hydrochloride with adrenaline solution, without hyaluronidase resulted in lid edema and conjunctival chemosis.

8. All solutions had comparable systemic safety profiles.

Therefore alkalinized lignocaine hyaluronidase solution is found to be superior to the other two solutions. A solution as efficacious as this minimizes the likelihood of supplementary injections, thereby preventing the added risk with each prick. Alkalinization is safe as no untoward systemic side effects were noted.

Also hyaluronidase can be used more effectively if the solution is alkalinized to near physiologic pH. Hyaluronidase can be excluded from the injectate avoiding its rare allergic complications, if the solution is not being alkalinized.

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WORKING PROFORMA

Name / Address

Age /Sex

Diagnosis

Operation Performed

Pre-Op Evaluation :

Ocular	**Systemic**
Vision/Refraction	Pulse
Tension	B.P.
Syringing	Chest
S/L	CVS
Fundus	
MFT	

Investigation:

Blood Sugar

Urine Examn

Anaesthesia Used – L A P/B technique

Group 1	Group 2	Group 3
8 ml 2% lignocaine with adr. + 50 IU/ml hyaluronidase (pH = 3.45)	8 ml of alkalinized 2% lignocaine with adr. (pH = 6.5)	8 ml of alkalinized 2% lignocaine with adr. + 50 IU/ml hyaluronidase (pH = 6.5)

Parameters Recorded

1) Time to onset of akinesia (minutes)

< 2 min	8 – 10 min
2 – 4 min	10 -12
4 – 6 min	12 – 15
6 – 8 min	> 15 min

2) Supplementary Anaesthesia Required

Yes No

3) Residual Movement (at the end of 15 min)

Yes No

Direction – up :

down :

in :

out :

4) Duration of akinesia and anaesthesia : Lasting for full surgery

Yes No

5) Post – Injection Thrust (subjective to surgeon)

None

Minimal

Moderate

Substantial Thrust

6) Conjunctival Chemosis

None

Mild (= 1 Quadrant)

Moderate (= 2 Quadrants)

Severe (>2 Quadrants)

7) Lid Edema

Present Absent

8) Post – Operative subjective onset of pain

30 min

1 hour

1 ½ hour

2 hour

9) Duration of Surgery (in Minutes)